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10/523,328	06/13/2005	Jun Kuai	WYTH-P01-001	8048

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EMCH, GREGORY S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,328	KUAI ET AL.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007 and 11 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,17,22-25,33-37,39 and 44-56* is/are pending in the application.

4a) Of the above claim(s) *3,4,6,7,9,10,24,33-37,39 and 44-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,11,12,17,22,23 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-12,17,22-25,33-37,39 and 44-56* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/13/05; 01/23/06*.

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application

6)☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election of Group I, claims 1-12, 17 and 22-25, in the reply filed on 05 October 2008 is acknowledged. The traversal is on the ground(s) that there would be no serious search burden to search Groups I-III together. This is not found persuasive because unity of invention, and not search burden is the issue. 37 CFR 1.475 (a) indicates that a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. 37 CFR 1.475(e) indicates that the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim (MPEP R-90 -- R-91 and 1893.03(d)).

Applicants elected the invention of Group I, claims 1-12, 17 and 22-25, drawn to an isolated, purified, or recombinant protein complex comprising: (i) a tumor necrosis factor alpha (TNF-α) polypeptide or a functional variant thereof; (ii) a TNF-α receptor (TNFR) polypeptide or a functional variant thereof; and (iii) at least one polypeptide

selected from the group consisting of: NF-κB activating kinase (NAK), RasGAP3, TRCP 1, TRCP2 and a functional variant thereof. 37 CFR 1.475 (b) describes the combinations of categories, which will be considered to have unity of invention when applications contain claims to different categories of invention. Accordingly, the claims of Groups II and III were not joined with the claims of Group I because the inventions of Groups I-X were found to have no special technical feature that defined the contribution over the prior art.

As set forth in the restriction requirement of 27 August 2007, the protein complex of Group I lacks a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The technical feature in the instant claims is that they all relate to an isolated, purified, or recombinant protein complex comprising: (i) a tumor necrosis factor alpha (TNF-α) polypeptide or a functional variant thereof; (ii) a TNF-α receptor (TNFR) polypeptide or a functional variant thereof; and (iii) at least one polypeptide selected from the group consisting of: NF-κB activating kinase (NAK), RasGAP3, TRCP 1, TRCP2 and a functional variant thereof. As stated previously, Heyninck et al. (Mol Cell Biol Res Commun. 2001 Sep;4(5):259-65; Cite No. CI on IDS dated 13 June 2005) teaches protein complexes comprising TNF-α, a TNFR and NAK (entire document, e.g., figs. 1 and 2). Thus, the technical feature linking the inventions of Groups I-X does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art. Thus, the product of Group II and the method of Group III combined with the product of Group I does not define a contribution over the prior art.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' election of the species TRCP1 in the reply filed on 05 October 2007 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' election of the species TNFR1 in the reply filed on 11 March 2008 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants' election of the species TRAP2 in the reply filed on 11 March 2008 is acknowledged. Because applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 3, 4, 6, 7, 9, 10, 24, 33-37, 39 and 44-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim. Applicants timely traversed the restriction requirement only in the reply filed on 05 October 2007.

Claims 1, 2, 5, 8, 11, 12, 17, 22, 23 and 25 are under examination in the instant office action.

Information Disclosure Statements

Signed and initialed copies of the IDS papers filed on 13 June 2005 and 23 January 2006 are enclosed in this action.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5, 8, 11, 12, 17, 22, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants are directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to an isolated, purified, or recombinant protein complex comprising: (i) a tumor necrosis factor alpha (TNF-α) polypeptide or a functional variant thereof; (ii) a TNF-α receptor (TNFR) polypeptide or a functional variant thereof; and (iii) at least one polypeptide selected from the group consisting of: NF-κB activating kinase (NAK), RasGAP3, TRCP 1, TRCP2 and a functional variant thereof.

Because the claims are drawn to functional variants of all of the recited polypeptides, these are genus claims. To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, there is no identification of any particular portion of the structure that must be conserved and there is no claimed function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the wild type polypeptides explicitly claimed, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated, purified or recombinant protein complexes comprising the wild type polypeptides claimed, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 1, 2, 5, 8, 11, 12, 17, 22, 23 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated, purified, or recombinant protein complex comprising: (i) a tumor necrosis factor alpha (TNF-α) polypeptide (ii) a TNF-α receptor (TNFR) polypeptide and (iii) at least one polypeptide selected from the group consisting of: NF-κB activating kinase (NAK), RasGAP3, TRCP 1, TRCP2, does not reasonably provide enablement for an isolated, purified, or recombinant protein complex comprising functional variants of the polypeptides mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claims 1, 2, 5, 8, 11, 12, 17, 22, 23 and 25 require the use of a broad genus of polypeptides, and as stated above, Applicants have not described all of the common features of the genus such that the skilled artisan could identify individual members. Applicants have not provided sufficient guidance, for example by showing a correlation between amino acid structure and any particular property to allow a skilled artisan to make and use protein complexes, which meet the limitations of the claims. There are no working examples involving the use of any variant encompassed by the claims, and there is no guidance as to any particular structure that must be conserved.

The potential amino acid sequences encompassed by the claims have particular structures, the predictability of which is complex and outside the realm of routine experimentation. Since detailed information regarding the structural requirements of the multitude of potential amino acid sequences encompassed by the claims are lacking, and given the lack of working examples reciting any of the variants encompassed by the claims, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, making and using said variants would constitute undue experimentation.

The art supports the unpredictability of the full scope of the claimed invention as

it teaches that even closely related members of the TNF superfamily have divergent functions (see Locksley et al. The TNF and TNF receptor superfamilies: integrating mammalian biology. Cell. 2001 Feb 23;104(4):487-501). It is also know that a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (see Yan et al. Science 290: 523-527, 2000).

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Due to the massive quantity of experimentation necessary to make and use the plurality of protein products encompassed by the claims, the absence of actual working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the claims, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and use the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 8, 17, 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Heyninck et al. (Mol Cell Biol Res Commun. 2001 Sep;4(5):259-65; Cite No. CI on IDS dated 13 June 2005).

The claims are drawn to an isolated, purified, or recombinant protein complex comprising: (i) a tumor necrosis factor alpha (TNF-α) polypeptide or a functional variant thereof; (ii) a TNF-α receptor (TNFR) polypeptide or a functional variant thereof; and (iii) at least one polypeptide selected from the group consisting of: NF-κB activating kinase (NAK), RasGAP3, TRCP 1, TRCP2 and a functional variant thereof

The Heyninck et al. reference teaches that the TNF-α ligand–receptor protein complex comprises TNF-α, TNFR1 and TRAF2 (e.g., fig.1). The reference teaches that TRAF2 interacts with NAK (referred to as NIK by the reference, e.g., fig.2) and with TRADD (p.259, second paragraph). Although the reference does not explicitly disclose the entire protein complex in one figure, for example, the reference inherently teaches said complex in its description of the different components of the TNF-α signal transduction pathways (entire document, especially pp.259-261), thus meeting the limitations of claims 1, 2, 8, 17, 22 and 23. For example, the reference teaches the first

portion of the complex in figure 1 and the second portion of the complex in figure 2, for example.

Since the reference teaches all the elements of the claims, claims 1, 2, 8, 17, 22 and 23 are anticipated by Heyninck et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 12, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heyninck et al as applied to claims 1, 2, 8, 17, 22 and 23 above, and further in view of Einhauer et al. (The FLAG peptide, a versatile fusion tag for the purification of recombinant proteins. J Biochem Biophys Methods. 2001 Oct 30;49(1-3):455-65).

The Heyninck et al. reference teaches as set forth above but does not teach the TNF or TNFR as fusion proteins. However, the Einhauer et al. reference teaches the versatility of the FLAG peptide as a fusion tag for the purification of recombinant proteins (entire document).

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosure of the TNF-TNFR protein complex taught by Heyninck et al. with the disclosure of FLAG fusion proteins taught by Einhauer et al. The skilled artisan would have been motivated to make these modifications for *in vitro* studies and provide TNF ligand-FLAG and/or TNFR-FLAG fusions because of the advantages of doing so as taught by Einhauer et al., e.g. ease of isolation, increased stability of fusion and enhanced expression level (entire document, e.g. p.458). The person of ordinary skill in the art would have had a reasonable expectation of success because the Einhauer et al. reference teaches that the fusions would work (entire document).

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

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Patent Examiner
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03 July 2008

/Elizabeth C. Kemmerer/
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